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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/359,920	07/22/99	GREEN	H H0535/7009(E

HM22/0521

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EXAMINER	
NAFF, D	
ART UNIT	**PAPER NUMBER**
1651	13

DATE MAILED: 05/21/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/359920	Breen et al
Examiner	Group Art Unit
Hafft	1657

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 3/9/01.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 55, 57, 66, 67, 71 + 74-112 is/are pending in the application.

Of the above claim(s)_____ is/are withdrawn from consideration.

☐ Claim(s)_____ is/are allowed.

☒ Claim(s) 55, 57, 66, 67, 71 + 74-112 is/are rejected.

☐ Claim(s)_____ is/are objected to.

☐ Claim(s)_____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on_____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on_____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)_____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:_____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 10 (Filed 12/19/00) ☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892 ☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948 ☐ Other_____

Office Action Summary

The amendment of 3/9/01 has been entered. The amendment amended the specification, canceled claims 53 and 65, amended claims 55, 57, 66, 67, 77-80, 82-85, 91, 94 and 97, and added claims 99-112.

Claims examined on the merits are 55, 57, 66, 67, 71 and 74-112 which are all claims in the application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 71, 74-76, 81 and 86-93 are objected to because of the following informalities: the claims depend on canceled claim 53 or 65. Appropriate correction is required.

Claims 102 and 103 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification fails to support the conjugate being in or on a microparticle. The specification at page 8, lines 17-20, discloses the agent being in a microparticle. This does not support the conjugate being in or on the microparticle or the agent being on the microparticle.

Claims 55, 57, 67, 71, 74-81, 82, 85-93, 95, 97-99, 104-108, 111 and 112 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 71, 74-76, 81 and 86-93 are confusing and unclear by depending on canceled claim 53 or 65. Additionally, in claim 76 "polymer

specification may define this limitation as having at least 20% glutamine, the term in the claims can have other meanings, and the claims rather than the specification define the metes and bounds of the invention.

Claims 67, 111 and 112 are confusing by requiring the polymer of claim 66 to comprise amino acids since claim 66 requires the polymer to contain amino acids. It is suggested that claim 67 be amended by canceling "comprises" in line 1 and inserting -- is a polymer of --, and at the end of the line cancel "and". Claims 111 and 112 should be similarly amended.

Claims 86, 89, 92, 95 and 98 are unclear by requiring the linking molecule in the third container to be covalently attached to the composition in the first container if in the presence of transglutaminase. Since the linking molecule and composition are in separate containers, it is impossible for them to be covalently attached in the presence of transglutaminase. It is suggested that claim 86 be amended in line 2 by inserting -- capable of -- before "covalently", and changing "attached" to -- attaching --, and in line 3, cancel "if", and after "transglutaminase" insert -- when the composition and linking molecule are not in the containers --. This change should also be made to claims 89, 92, 95 and 98.

Claim 55 and claims dependent thereon are confusing and unclear by "linking molecule is not native to the agent" in line 9 of claim 55 being uncertain as to meaning and scope. Does this mean that the linking molecule is different from the agent or does it mean something else?

U.S.C. 103(a) as being unpatentable over Richardson et al (5,490,980) in view of Kahlem et al (CD), Greenberg et al (CF) and Davies et al (CA), and if necessary in further vies of Green et al (5,525,336) for type of reasons set forth in the previous office action of 10/3/00.

Claim 55 and claims dependent thereon are drawn to a conjugate of a nonextracellular matrix, nonlabeling agent and a carboxamide-carrying linking molecule that is not native to the agent, contains at least two contiguous linked glutamines and is a substrate of transglutaminase.

Claim 66 and claims dependent thereon require a conjugate of the agent and a polymer that contains at least three contiguous lysines attached to one another by peptide bonds and is a substrate of transglutaminase. Also claimed are kits having a first container containing the conjugate of claim 55 or 66 and a second container containing transglutaminase, and additionally a kit containing a third container containing a linking molecule.

Richardson et al disclose (col 2, lines 44-58) a composition containing an active ingredient modified to contain an $-RNH_2$ moiety where R is a straight aliphatic hydrocarbon chain of 1 to 8 carbon atoms and preferably at least 5 carbon atoms. Transglutaminase uses the $-RNH_2$ moiety as a substrate to bind the active ingredient through the $-RNH_2$ moiety to glutamine residues in skin, hair or nails. Most preferably the active ingredient contains more than one $-RNH_2$ moiety in order to obtain enhanced binding of the active ingredient.

Kahlem et al, Greenberg et al and Davies et al disclose transglutaminase crosslinking by acting on carboxamide-containing

Green et al disclose transglutaminase crosslinking proteins together by forming bonds between glutaminyl and lysyl residues.

It would have been obvious to link the active agent of Richardson et al to a carboxamide-containing substrate of transglutaminase since it would have been expected from Kahlem et al, Greenberg et al and Davies et al that this substrate will substitute for the function of the $-RNH_2-$ containing moiety of the active agent of Richardson et al by the transglutaminase catalyzing a reaction between a carboxamide of peptide-bound glutamine and a primary amino group (RNH_2) of peptide-bound lysine. As to claim 65, the $-RNH_2$ moiety of Richardson et al is an aliphatic amine. To provide a polymer such as a lysine-containing protein or peptide having the $-RNH_2$ moiety for attaching the active ingredient of Richardson et al would have been a matter of obvious choice since it would have been apparent from Kahlem et al, Greenberg et al and Davies et al that the carboxamide group and the primary amino group of RNH_2 can both be contained by a peptide or protein, and that crosslinking or attachment will occur irrespective of which protein or peptide contains the active ingredient. Forming a kit as required in claims 71 and 86-98 would have been obvious to provide the active ingredient of Richardson et al in a form ready to use for bonding to skin, hair or nails. Having transglutaminase in a separate container would have been obvious to prevent its acting on the substrate before crosslinking is desired. If needed, Green et al would have further suggested that different substrates for transglutaminase can be used.

Applicant's arguments filed 3/9/01 have been fully considered but

Applicants urge that in Richardson et al the active agent and transglutaminase must be simultaneously applied to skin, hair or nails. However, the present claims are drawn to a conjugate and not to a method, and the claims do not exclude applying the active agent and transglutaminase simultaneously.

Applicant urge that the alkylamine groups of Richardson et al are applied individually to the active agent, and not directly conjugated to each other. However, Kahlem et al disclose that polyglutamine is a substrate for transglutaminase, and it would have been obvious to provide the alkylamine as a polyglutamine or a polylysine. This is further suggested by Green et al crosslinking corneocyte proteins that are polyamino acids with transglutaminase. It is recognized that Davies et al disclose that transglutaminase is specific for protein bound glutamine. However, the present claims do not exclude protein bound glutamine. Moreover, Kahlem et al disclose that a glutamine bearing peptide such as a synthetic polyglutamine polypeptide acts as a substrate for transglutaminase. The claims clearly do not exclude a synthetic polyglutamine and polylysine. It would have been expected from the references that when the linking molecule, agent and/or polymer of the claims is a polyglutamine or polylysine, crosslinking will occur in the presence of transglutaminase. In claim 55, the linking molecule can be a polyglutamine and in claim 66, the polymer can be polylysine. To attach the active ingredient of Richardson et al to polyglutamine or polylysine to provide the alkylamine groups would have been a matter of obvious choice depending on individual preference. While the glutamine of

been obvious when the other references are considered that the active ingredient can be attached to a protein or synthetic polypeptide that contains lysine residues when the active ingredient is modified to contain glutamine residues. An unexpected result has not been established in the use of at least two contiguous linked glutamines and at least three contiguous linked lysines in conjugates as claimed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is (703) 308-0520. The examiner can normally be reached on Monday-Thursday and every other Friday from about 8:30 AM to about 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, a message can be left on voice mail.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn, can be reached at telephone number (703) 308-4743.

The fax phone number is (703) 305-3014 or 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

DAVID M. NAFF
PRIMARY EXAMINER
ART UNIT 1651

DMN
5/18/01